Author's response to reviews

Title: A Modified Regimen of Extracorporeal Cardiac Shock Wave Therapy for Treatment of Coronary Artery Disease

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Author's response to reviews: see over
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Editorial Team
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Dear Editor:

We are submitting a revision of our manuscript ID 1932547859709095, entitled “A Modified Regimen of Extracorporeal Cardiac Shock Wave Therapy for Treatment of Coronary Artery Disease” and hope that the revision is now suitable for publication in your journal. A list of specific changes made in response to the reviewers’ comments can be found below.

Sincerely,

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Referee 1:
**Reviewer’s report**

There are some major questions and remarks:
1. The authors used peak systolic tissue Doppler-based strain rate (PSSR) under resting and load conditions and they could demonstrate an improvement with CSWT. Some readers might be sceptically about the reproducibility of tissue Doppler SR data in your study - please give us some data of your echo lab regarding inter- and intraobserver variability. PSSR was measured in all 17 segments, or in middle and basal segments?

**Reply:** To answer these questions, we have added the following material to the Methods section:
“a) One of authors of this paper carried out the PSSR measurement for all patients during the entire follow-up period. However, that author did not know the treatment of each patient. Before this study, that author conducted a preliminary study on the feasibility and repeatability of PSSR measurement of all 16 segments of the left ventricle and the results showed no statistically significant difference (P> 0.05).
b) Before CSWT treatment, radionuclide imaging and stress echocardiography were used to locate the ischemic segments in each patient. These segments might be the middle or the apical segment of interventricular septum, or the lateral basal segment. The PSSR was measured in the specific ischemic segments.”
2. What is really new of this study: only the modification of CSWT application (3 vs 1 month) – is this enough for a new publication?

Reply: Novelty: The first series of studies on the use of CSWT for the treatment of coronary heart disease were carried out in China; the CSWT group and drug treatment control group were compared. In addition to the radionuclide MPI, the ischemic myocardium was positioned using the dobutamine stress echocardiography. Our research team is the first to develop one-month intensive therapy, which has similar efficacy as the classic 3-month sequential CSWT protocol. Our CSWT protocol saves time and cost and has better compliance, which is more suitable for China.

To emphasize the novelty and potential clinical importance of the new CSWT protocol, we have added the following sentence to the Introduction: ”A one month protocol has not previously been developed, but a shorter protocol would save time and cost, produce better compliance, and might be a more suitable protocol than a three month protocol in China.”

3. The authors should discuss the usage the PSSR instead of 2D strain or global 2D strain measurements using the papers of Voigt et al. using PSSR and postsystolic shorting in stress echocardiography.

Reply: We have added the following paragraph and references to the Discussion section.

PSSR has higher temporal and spatial resolution than M type imaging. Voigt’s study showed that the peak systolic strain rate (PSSR) in the long-axis view decreased with the deterioration of the wall motion. Its sensitivity for determining the myocardial ischemia was 86% under the dobutamine stress test and its specificity was 90%. However, compared with the latest 2D-strain testing, PSSR is affected by the angle and can only measure the radial strain in the apical four-chamber and apical two-chamber view. It cannot measure the strain in the short-axis view. The present study selected PSSR to assess the local cardiac function because it was the most mature method available at the beginning of the study. Our research team members have used it for many years, so systematic errors can be reduced. Another reason for using PSSR is that we use GE VV7 instrument in our lab, and it has complete TDI and strain rate imaging software. The 2D-strain requires the SIMENS Sequia 512 instrument, and that instrument was not introduced until the late stage of this study. Therefore, in order to keep the consistency of results, we did not change the measurement indices.


4. Page 12: the last section is not very clear: “…PSSR after load and resting MPI were…”

Reply: This study used two imaging methods to evaluate myocardial function and blood supply status. One was PSSR measurement in ultrasound scan, and the other was radionuclide MPI imaging. They were measured in the basal state and under dobutamine stress, respectively. "PSSR after the load and the resting the MPI were" means that patients were followed up for one month after 9 times of treatment, and the PSSR under stress and the MPI in the basal state were improved significantly in the 25 patients. We have reworded the description to make the meaning more clear.

Referee 2:

Reviewer's report:

However, some major concerns have to be addressed:
1. The number of patients in the subgroups is very small, particularly only 10 pts of group B completed the 12 months follow-up. Why? At least this should be explained and mentioned in the manuscript. Furthermore, please add a sufficient limitation section.

Reply: The protocol for group B was the one-month intensity treatment that was developed by our research team in the middle of this study. Therefore, 11 of 21 patients in group B had not been followed up for 12 months at the time the paper was written. That is why they were missed. We have added this as a limitation.

2. The comparisons in all tables are very confusing (p, §,* , a,b,...). Please simplify. A figure would be much more interesting. Table 3 adds no information, only that you observed no changes in the standard echo parameters. Please shorten or delete this table.

Reply: The labeling on Table 2 has been simplified. $P<0.05$, indicates significant difference when compared with month 0 of the corresponding group. Table 3 has been deleted.

3. Please provide echo figures demonstrating how you determine the amplitude of regional myocardial motion, and PSSR measurements.

Reply: A new Figure 1 has been added to show how we determined the amplitude of regional myocardial motion. The amplitude of regional myocardial motion is the range of motion measured using the M-type. PSSR refers to the measurement of the peak systolic strain rate using tissue Doppler imaging.
4. Please simplify tables 4 and 5. Add some figures instead.

**Reply:** Old Tables 4 and 5 have been converted as NEW Figures 2 and 3, respectively.

Minor concerns:

Please explain the abbreviations in table 1 (EH, AF, UC, CRF, ...)

**Reply:** EH: essential hypertension, COPD: chronic obstructive pulmonary diseases, CRF: chronic renal failure, AF: atrial fibrillation; UC: ulcerative colitis. We have replaced the abbreviations with the full names in Table 1, except for COPD, where we have added the full name in a footnote.

Have you some other objective data for working capacity than 6 MWT (ergometry, ...). Please provide these data.

**Reply:** In addition to 6MWT, we also conducted the treadmill test for working capacity. However, only some patients in each group were subjected to the treadmill test. Since the N values for treadmill test are different from those of the rest of this study, the treadmill test data are presented as a supplementary Table. We have added this supplementary Table and mentioned it briefly in Results.

There are typing errors in paragraph "grouping" page 5, please check

**Reply:** This paragraph has been edited for errors.